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# Cigarette smoking and breast cancer risk: update of a prospective cohort study

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**Abstract** The results of epidemiologic studies of the association between cigarette smoking and breast cancer risk have been inconsistent. In spite of the inconsistency, several recent analyses have suggested an increased risk of breast cancer among women who smoked cigarettes for a long period of time and/or who started smoking before their first pregnancy. Our analyses were conducted in the Canadian National Breast Screening Study (NBSS), a multi-center, randomized controlled trial of mammographic screening for breast cancer among 89,835 women aged 40–59 at enrollment. Participants were recruited between 1980 and 1985 from the general Canadian population. During an average of 16.1 years of follow-up, we identified 4,445 incident breast cancer cases. We used the Cox proportional hazards models to estimate multivariate rate ratios (RRs) and 95% confidence limits (CLs) for the association between cigarette smoking and breast cancer. We found that breast cancer risk was associated with the duration (40 years versus 0: RR = 1.50, 95% CL = 1.19, 1.89), intensity (40 cigarettes per day versus 0: RR = 1.20, 95% CL = 1.00, 1.44), cumulative exposure (40 pack-years versus 0: RR = 1.17, 95% CL = 1.02, 1.34), and latency of cigarette smoking (40 years since commencement of smoking versus 0: RR = 1.28, 95% CL = 1.06, 1.55), as well as smoking initiation before a first full-term pregnancy (among parous women, more than 5 years of smoking versus 0: RR = 1.13, 95% CL = 1.01–1.25). These results strongly suggest that cigarette smoking might play an important role in the etiology of breast cancer, particularly when initiated relatively early in life and when engaged in for long durations.

**Keywords** Smoking · Breast cancer · Risk · Cohort study

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## Introduction

In vitro, in vivo, and human biomarker studies have strongly suggested that breast tissue is a target for the carcinogenic effects of tobacco smoke [1]. Carcinogens found in tobacco smoke can pass through alveolar membrane and be transported to the breast tissue by plasma lipoproteins [2, 3]. Due to their affinity for lipids, tobacco-derived carcinogens can be stored in breast adipose tissue and then bioactivated by human mammary epithelial cells [4]. Tobacco smoke-specific DNA adducts are more common in the breast tissue of smokers than that of nonsmokers [5–7]. Furthermore, cigarette smoking appears to increase the prevalence of *p*53 gene mutations in breast tumors and the differences in the mutational spectrum between smokers and nonsmokers are consistent with those found in lung cancer [1]. These studies support the biological plausibility of a detrimental effect of cigarette smoking on breast cancer risk. In contrast, cigarette smoking also appears to have antiestrogenic effects, given that, when compared with non-smokers, smokers have reduced bone density [8, 9], an earlier age at menopause [10],

reduced urinary levels of estrogen [11], and an attenuated effect of hormone replacement therapy (HRT) [9]. Since estrogen is a well-established risk factor for breast cancer [12], cigarette smoking might protect against breast cancer due to its antiestrogenic effects.

To date, results of epidemiologic studies of the association between cigarette smoking and breast cancer risk have been inconsistent, with positive, inverse, and null associations found in different studies [13]. In spite of the inconsistency, several recent analyses have suggested an increased risk of breast cancer among women who smoked cigarettes for a long period of time and/or who started smoking before their first pregnancy [14–18]. In 2002, our group published results on cigarette smoking and breast cancer risk in the Canadian National Breast Screening Study (NBSS), in which 89,835 women were followed for an average of 10.6 years and 2,552 incident cases of breast cancer were identified during the follow-up period [14]. We demonstrated that women with a history of long-term cigarette smoking had an increased risk of breast cancer. Here we provide updated results on cigarette smoking and breast cancer risk among this large cohort, with an average follow-up period of 16.1 years and a total of 4,445 incident breast cancer cases.

## Methods

### Study population

The study design has been described in detail elsewhere [19, 20]. Briefly, the NBSS is a multi-center, randomized controlled trial of mammographic screening for breast cancer among 89,835 women aged 40–59 at enrollment. Participants were recruited between 1980 and 1985 from the general Canadian population. Incident cases of breast cancer and deaths from all causes were ascertained by means of computerized record linkages to the Canadian Cancer Database and to the National Mortality Database, both of which are maintained by Statistics Canada. The linkages to the databases yielded data on cancer incidence and mortality to December 31, 2000 for women in Ontario, December 31, 1998 for women in Quebec, and December 31, 1999 for women in other provinces in Canada. The average follow-up period for the cohort was 16.1 years, during which there were 4,445 incident breast cancer cases, among whom 4,434 had smoking data collected at enrollment. The NBSS was approved by the appropriate Institutional Review Boards. Informed consent was obtained from all study participants.

### Questionnaires

Upon enrollment in the NBSS, all participants completed self-administered questionnaires that sought information on demographic characteristics, lifestyle factors (including cigarette smoking), menstrual and reproductive history, use of oral contraceptives (OCs) and use of HRT. Starting in 1982, a questionnaire regarding dietary intake (including alcohol consumption) and physical activity was distributed to all new participants and to participants who returned to the screening centers for rescreening. By the time that the diet and physical activity questionnaire was introduced, some women had already been enrolled in the study and were not seen again at the screening centers. A total of 49,613 women completed the questionnaire regarding diet and physical activity.

Regarding the history of cigarette smoking, participants were first asked whether or not they had ever smoked. Women who had smoked were then asked how many cigarettes they smoked per day and how many years they had smoked. If women were former smokers, they were asked the year they had ceased smoking. Age at which smoking commenced was calculated by subtracting the total years of smoking from the age at recruitment for current smokers and by subtracting the total years of smoking and the time since quitting smoking from the age at recruitment for ex-smokers. Pack-years of smoking were calculated by multiplying the total years of smoking by the number of cigarettes smoked per day divided by 20.

### Statistical analysis

Participants contributed person-time to the study from their date of enrollment until the date of diagnosis of breast cancer, the date of death, or the end of follow-up period, whichever came first. We used the Cox proportional hazards models to estimate rate ratios (RRs) and 95% confidence limits (CLs) for the association between cigarette smoking and breast cancer. In multivariate analyses, we controlled for age at enrollment (5-year age groups), randomization group (intervention versus control), study center, body mass index (BMI) at baseline (quartiles), education level (less than high school, high school, and university), vigorous physical activity (h/day: 0, >0–1, >1, with a separate category for missing), OC use (never + 4 levels of duration), use of HRT (never + 4 levels of

duration), parity (0, 1–2, 3–4, 5+), age at menarche (<12, 12, 13, 14+), history of benign breast disease (yes, no), practice breast self-exam (yes or no), family history of breast cancer in first-degree relatives (yes, no), menopausal status (pre, peri, post), and alcohol consumption (g/day: 0, >0–14, >14, with a separate category for missing). Since BMI might be a confounder or a mediating variable [14], we also analyzed the data without control for BMI in multivariate models. We found that removing BMI did not affect the estimates appreciably.

For tests of trend in risk across successive levels of categorical variables, successive integers were fitted in the risk models. Tests for interaction were based on the likelihood ratio tests comparing models with or without product terms representing the variables of interest. The likelihood ratio test that all of the interaction parameters were 0 was conducted by referring 2* the absolute difference in the log likelihoods of models with or without interaction terms to the $X^2$ distribution on degrees of freedom equal to the number of interaction parameters. All analyses were performed in SAS 9.1 (SAS Institute, Cary, NC). *P*-values were two-sided.

## Results

Current smokers had an 18% increase in breast cancer risk (HR = 1.18, 95% CL = 1.09, 1.27) whereas former smokers were not at altered risk (HR = 1.00, 95% CL = 0.93, 1.08). Smoking intensity, smoking duration, pack-years of cigarette smoking, and years since smoking commenced were positively associated with breast cancer risk and the associated trends were statistically significant (Table 1). The highest breast cancer risk was found among women who smoked 40 years or more (RR = 1.50, 95% CL = 1.19, 1.89). We found that age at which smoking commenced was inversely associated with breast cancer risk (*P* for trend = 0.01). In addition, no clear association between years since quitting smoking and breast cancer risk was found (*P* for trend = 0.43), although women who had quit smoking recently (within 9 years) showed a slight reduction in breast cancer risk when compared to current smokers.

When analyses were restricted to parous women, we found a dose-response relationship (*P* for trend = 0.041) between duration of smoking prior to the first full-term pregnancy and risk of breast cancer (Table 2). In contrast, there was no evidence of a dose–response relationship for duration of smoking after a first full-term pregnancy (*P* for trend = 0.10).

Consistent with the results presented in our previous report [14], we found no modification of the association between cigarette smoking and breast cancer by menopausal status, alcohol consumption, BMI, duration of HRT use, age at menarche, duration of OC use, parity, family history of breast cancer, history of benign breast disease, and randomization assignment (data not shown). In contrast, we found some suggestion that vigorous physical activity might modify the effect of cigarette smoking on breast cancer (Table 3). The positive associations of breast cancer with smoking intensity, smoking duration, pack-years of cigarette smoking, and years since smoking commenced were mainly present among women who did not report vigorous physical activity.

## Discussion

The results of epidemiologic studies of the association between cigarette smoking and breast cancer risk have been inconsistent. Our group reviewed epidemiologic studies up to 2002 and concluded that smoking appears not to decrease breast cancer risk [13]. Indeed, there is some evidence for an increased risk of breast cancer with smoking of long duration and with smoking before a first full-term pregnancy. Since the publication of our review paper, five population-based case–control studies [16, 17, 21–23] and three cohort studies [18, 24, 25] have investigated the association between duration of smoking and breast cancer risk. Among them, three of the case-controls studies [16, 17, 23] and all cohort studies [18, 24, 25] observed an increase in breast cancer risk with long-term cigarette smoking. In addition, two population-based case–control studies [16, 17] and five cohort studies [15, 18, 24–26] have assessed the association between smoking before a first full-term pregnancy and breast cancer risk. Among them, all of the case–control studies [16, 17] and four of the cohort studies [15, 18, 24, 25] associated smoking before a first full-term pregnancy with increased risk of breast cancer.

In our large cohort study, we found positive associations of breast cancer risk with smoking duration, intensity, cumulative exposure, and latency. These associations suggest that cigarette smoking might have carcinogenic effects on the breast. Furthermore, the plausibility of the effects is enhanced by the dose–response relationships that were observed between the above-mentioned smoking measures and breast cancer risk. In contrast to our previous report, we found an inverse association between the age at which smoking commenced and breast cancer risk. We also found

**Table 1** Adjusted RRs for breast cancer in relation to cigarette smoking among women in the NBSS

| Smoking measure | Cases/person-years | RR (95% CL)[a] |
|---|---|---|
| *Cigarettes/day* | | |
| Never-smokers | 2249/759,491 | 1.0 (referent) |
| 1–9 | 475/156,447 | 1.02 (0.92, 1.13) |
| 10–19 | 591/190,241 | 1.06 (0.96, 1.16) |
| 20–29 | 848/260,424 | 1.12 (1.03, 1.21) |
| 30–39 | 145/46,199 | 1.08 (0.92, 1.28) |
| 40+ | 126/36,192 | 1.20 (1.00, 1.44) |
| | | $P_{trend}$ = 0.0018 |
| *Years smoked* | | |
| Never-smokers | 2249/759,491 | 1.0 (referent) |
| 1–9 | 362/124,937 | 1.00 (0.90, 1.12) |
| 10–19 | 507/173,293 | 1.02 (0.93, 1.13) |
| 20–29 | 761/244,544 | 1.09 (1.00, 1.19) |
| 30–39 | 453/125,060 | 1.14 (1.03, 1.27) |
| 40+ | 77/14,371 | 1.50 (1.19, 1.89) |
| | | $P_{trend}$ = 0.0003 |
| *Pack-years* | | |
| Never-smokers | 2249/759,491 | 1.0 (referent) |
| 1–9 | 728/245,615 | 1.02 (0.93, 1.11) |
| 10–19 | 466/156,318 | 1.02 (0.92, 1.13) |
| 20–29 | 388/120,485 | 1.13 (1.02, 1.27) |
| 30–39 | 332/91,725 | 1.21 (1.07, 1.36) |
| 40+ | 246/68,062 | 1.17 (1.02, 1.34) |
| | | $P_{trend}$ = 0.0002 |
| *Years since smoking commenced* | | |
| Never-smokers | 2249/759,491 | 1.0 (referent) |
| 1–9 | 74/25,312 | 1.01 (0.80, 1.28) |
| 10–19 | 283/97,372 | 1.05 (0.93, 1.19) |
| 20–29 | 916/320,650 | 1.04 (0.96, 1.12) |
| 30–39 | 761/209,977 | 1.13 (1.04, 1.23) |
| 40+ | 120/25,436 | 1.28 (1.06, 1.55) |
| | | $P_{trend}$ = 0.0023 |
| *Age smoking commenced* | | |
| Never-smokers | 2249/759,491 | 1.0 (referent) |
| 20+ | 1295/402,791 | 1.07 (0.99, 1.14) |
| 16–19 | 637/201,857 | 1.10 (1.01, 1.21) |
| <16 | 222/74,098 | 1.11 (0.97, 1.28) |
| | | $P_{trend}$ = 0.010 |
| *Years since cessation of smoking*[b] | | |
| Current smokers | 1051/312,187 | 1.0 (referent) |
| 1–9 | 514/177,781 | 0.87 (0.78, 0.97) |
| 10–19 | 405/125,956 | 1.00 (0.87, 1.15) |
| 20+ | 215/73,579 | 0.93 (0.76, 1.12) |
| | | $P_{trend}$ = 0.43 |

[a]Adjusted for age at baseline (in 5-year age groups), randomization group (intervention, control), study center, body mass index (quartiles), educational level (less than high school, high school, and university), vigorous physical activity (h/day: 0, >0–1, >1, with a separate category for missing), oral contraceptive use (never + 4 levels of duration), hormone replacement therapy (never + 4 levels of duration), parity (0, 1–2, 3–4, 5+), age at menarche (<12, 12, 13, 14+), history of benign breast disease (yes, no), practice breast self-exam (yes or no), family history of breast cancer in a first-degree relative (yes, no), menopausal status (pre, peri, post), and alcohol consumption (g/day: 0, >0–14, >14, with a separate category for missing)

[b]Former and current smokers only, with additional adjustment for duration of smoking

**Table 2** Adjusted RRs for breast cancer in relation to cigarette smoking before or after a first full-term pregnancy among parous women in the NBSS

| Years smoked | Cases/person-years | RR (95% CL)[a] |
|---|---|---|
| *Before first full-term pregnancy*[b] | | |
| 0 | 2420/854,506 | 1.0 |
| >0–5 | 578/199,741 | 1.01 (0.91, 1.13) |
| >5 | 588/173,055 | 1.13 (1.01, 1.25) |
| | | $P_{trend}$ = 0.041 |
| *After first full-term pregnancy*[c] | | |
| 0 | 1990/708,945 | 1.0 |
| >0–10 | 416/146,258 | 0.99 (0.88, 1.11) |
| >10–20 | 608/194,489 | 1.12 (1.01, 1.24) |
| >20 | 572/177,610 | 1.07 (0.96, 1.20) |
| | | $P_{trend}$ = 0.10 |

[a]Adjusted for the variables shown in the footnote to Table 1

[b]With additional adjustment for years of smoking after a first full-term pregnancy

[c]With additional adjustment for years of smoking before a first full-term pregnancy

some suggestion that vigorous physical activity might modify the effect of cigarette smoking on breast cancer risk. The fact that we observed no association with the age at which smoking commenced and no effect modification by vigorous physical activity in our previous report is likely due to the smaller number of breast cancer cases and shorter follow-up period.

The results of previous studies of the association between cigarette smoking before first pregnancy and breast cancer risk have been inconsistent, with seven studies showing positive associations and the remaining seven studies showing no association. A meta-analysis based on 11 studies published before or in early 2004 concluded that smoking prior to a first birth is not associated with increased risk of breast cancer [26]. However, this meta-analysis did not include three recent cohort studies, all of which observed positive associations [15, 18, 24]. Consistent with these cohort studies and the Nurses' Health Study published in 2002, our study demonstrated that smoking before a first full-term pregnancy was associated with a moderately increased risk of breast cancer. However, the association should be interpreted with caution due to the fact that women who started smoking before a first full-term pregnancy were likely to have started smoking at a younger age and to have a longer duration of smoking. Nevertheless, the biological plausibility of the positive association between smoking before a full-term pregnancy and breast cancer risk is supported by animal data and developmental characteristics of the human breast. Rodent models have demonstrated that

**Table 3** RRs and 95% CLs for breast cancer in relation to cigarette smoking stratified by vigorous physical activity[a]

| Smoking measure | Vigorous physical activity (h/day) | | | *P* for heterogeneity |
|---|---|---|---|---|
| | >1 | >0–1 | 0 | |
| Cigarettes/day[b] | 0.98 (0.94, 1.02) | 0.99 (0.95, 1.02) | 1.04 (1.00, 1.08) | 0.034 |
| Years smoked[b] | 1.01 (0.97, 1.05) | 0.99 (0.96, 1.03) | 1.04 (1.01, 1.08) | 0.13 |
| Pack-years[b] | 1.01 (0.97, 1.04) | 0.99 (0.96, 1.02) | 1.03 (1.01, 1.06) | 0.078 |
| Years since smoking commenced[b] | 0.98 (0.95, 1.02) | 1.00 (0.98, 1.03) | 1.04 (1.01, 1.07) | 0.035 |

[a]Adjusted for the variables shown in the footnote to Table 1. Analyses were restricted to women with data on vigorous physical activity

[b]Treating cigarette smoking as continuous variables; the estimated RRs correspond to the changes in risk in association with an increase of five cigarettes per day, 5 years of smoking, 5 pack-years of smoking, and 5 years since smoking commenced, respectively

certain chemical carcinogens induce mammary tumors in nulliparous females, but fail to induce tumors in parous females [27]. It has been hypothesized that the breast epithelial cells are especially sensitive to chemical carcinogens before a first full-term pregnancy due to the fact that the breast of nulliparous women is predominantly composed of undifferentiated ducts and lobules and that pregnancy can induce differentiation of the breast [28, 29]. Our study supports the concept that the timing of smoking initiation, particularly in relation to first full-term pregnancy, might play an important role in the development of breast cancer.

There is some evidence that women who exercise regularly have a reduced risk of breast cancer [30, 31]. In this study, there was some suggestion that vigorous physical activity might counteract the adverse effects of cigarette smoking on breast cancer risk. However, the assessment of physical activity in our study was limited as we only asked the participants to recall their physical activity in the past 1 month at baseline. We did not assess the lifetime physical activity, nor did we quantify each specific activity. This suggests the need for studies with better physical activity assessments to verify our results. In addition, the biological explanation for this potential effect modification by physical activity is unclear.

Among the strengths of our study are the prospective design, the large sample size, essentially complete follow-up of the cohort, and comprehensive data on risk factors for breast cancer, thereby minimizing selection bias and reducing the potential for uncontrolled confounding. However, our study is subject to certain limitations. Although we adjusted for many potential confounding factors, we cannot exclude the possibility that there was residual confounding resulting from error in the measurement of these variables (partially due to failure to collect their updated information during the follow-up period), and from other unmeasured variables. A further limitation is that we did not collect data on passive smoking and therefore were not able to control for it in multivariate analyses. However, failure to control for passive smoking might not be problematic. Although some case–control studies have observed an increased risk of breast cancer among passive smokers, large cohort studies have found no or little increase in risk [25, 32–34]. Given the fact that a proportion of non-smokers might have been exposed to passive smoking, the association between active smoking and breast cancer risk might be biased towards the null, if passive smoking were a risk factor for breast cancer but were not accounted for in the analyses. Indeed, several studies have demonstrated that exclusion of passive smokers from the reference group helped to reveal positive associations between cigarette smoking and breast cancer [18, 35, 36]. In contrast, a couple of studies found that exclusion of passive smokers from the reference group did not appreciably affect the risk ratio estimates for active smoking [25, 34]. Nevertheless, detailed information on passive smoking should be collected in future studies. Another limitation is that we did not collect updated information on smoking exposure, alcohol consumption, weight change, menopausal status, and hormone use during the follow-up period. Changes in smoking habits during follow-up may have lead to exposure misclassification and such non-differential misclassification is likely to have biased the estimates of risk towards the null [37]. In addition, failure to collect updated information on alcohol consumption, weight change, menopausal status, and hormone use might have limited our interpretation of their modifying effects on the association between smoking and breast cancer.

In conclusion, our large cohort study showed that breast cancer risk was associated with the duration, intensity, cumulative exposure, and latency of cigarette smoking, as well as smoking initiation before a first full-term pregnancy. These results strongly suggest that

cigarette smoking might play an important role in the etiology of breast cancer.

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